Remarks

Claims 61 and 70-93 are newly cancelled without prejudice to the right to pursue the cancelled subject matter of these claims in this or other patent applications. Claims 94-120 are newly added and are pending.

Newly added Claims 94-120 more clearly define the subject matter of the invention and properly fall within the subject matter of the elected claims. Support for newly added claims is found throughout the specification, and in the claims as originally filed. No new matter has been entered. All newly added claims are encompassed by Group I of the restriction requirement drawn to methods of identifying biomarkers for schizophrenia and methods for diagnosis and prognosis of schizophrenia, further restricted to the BTG2 gene.

Support for reciting comparison of biomarker RNA levels of a test subject with those of control subjects having a disease (i.e. schizophrenia) and with those of healthy control subjects, and determination of a statistically significant similarity or difference with a p value less than 0.5 can be found in the published application US 20040241727 (hereinafter "Published Application"), for example at paragraph [0127] ("*when comparing two or more samples for differences, results are reported as statistically significant when there is only a small probability that similar results would have been observed if the tested hypothesis (i.e., the genes are not expressed at different levels) were true. The accepted lower threshold is set at, but not limited to, 0.05 (i.e., there is a 5% likelihood that the results would be observed between two or more identical populations) such that any values determined by statistical means at or below this threshold are considered significant*"), at paragraph [0128] ("*when comparing two or more samples for differences, results are reported as statistically significant when there is only a small probability that similar results would have been observed if the tested hypothesis (i.e., the genes are not expressed at different levels) were true*").

Support for methods encompassing classification of a test subject level with specific control levels can be found, for example, at claim 15 as originally filed ("*d) determining whether the level of said one or more gene transcripts of step a) classify with the levels of said transcripts in step b) as compared with levels of said transcripts in step c) wherein said determination is indicative of said individual of step a) having schizophrenia.* "), at paragraph [0134] (relating to "*Methods that can be used for class prediction analysis*"), [0412] ("*Classification or class*

prediction of a test sample of an individual to determine whether said individual has schizophrenia or does not having schizophrenia can be done using the differentially expressed genes as shown in Table 3Y as the predictor genes in combination with well known statistical algorithms as would be understood by a person skilled in the art and described herein").

Specification

The specification [at Example 28, paragraphs 421 and 422, in the published application (US 2004/0241727 A1)] has been amended to accurately reflect that the relevant Chagas disease-related biomarkers in that example are listed in "Table 3Z", and not, as erroneously indicated, in "Table 3Y" which refers to the claimed schizophrenia biomarker. Reference should be made to "Table 3Z", and not to "Table 3Y", as evidenced in the table legends disclosed at paragraphs 208 and 209 of the published application which correctly indicate that Table 3Y relates to schizophrenia and Table 3Z relates to Chagas disease. In addition, there are 668 Chagas biomarker genes referred to at paragraph 421, and 668 genes are correspondingly listed in actual Table 3Z, whereas there are over 1,950 genes listed in Table 3Y. Thus, Applicant submits that this is merely a typographical error, and that correction of this typographical error is not new matter.

Claims rejections – 35 USC 112 1st paragraph, enablement

Claims 61 and 70-93 are rejected under 35 USC 112 1st paragraph, enablement Applicant respectfully traverses. Claims 61 and 70-93 have been newly cancelled by Applicant.

Applicant respectfully traverses to the extent that they apply to newly added claims 94-119. Applicant disagrees with the rejection's assertion that the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention in view of the breadth of the claims, the amount of guidance provided by the specification, and the level of predictability in the art.

The rejected claims include the steps of determining the level of RNA encoded by an BTG2 gene in a blood sample obtained from a human test subject and comparing it to the level of control RNA encoded by the gene in blood samples of control subjects, where the comparison is indicative of schizophrenia in said human test subject.

The rejection asserts that the claims are broad with respect to "control subjects", indicating that "control subjects" could encompass patients with schizophrenia, healthy patients, patients with some other disease such as depression, rheumatoid arthritis or multiple sclerosis (page 3 of the office action). The newly added claims recite two clearly defined sets of controls; subjects having schizophrenia and healthy controls.

The office action states that the claims are broad because they encompass any level and any direction of gene expression is indicative of schizophrenia (page 4 of the Office Action) and suggests that without providing this information, the mere observation of differences is an unpredictable indicator of schizophrenia.

The Applicant respectfully submits that the invention is taught in such terms that one skilled in the art can make and use the claimed invention, including the use of the elected biomarker BTG2 as an indicator of schizophrenia as described in the claims without disclosing the direction or the level of difference that exists between patients having schizophrenia and individuals not having schizophrenia. The Applicant has identified the elected gene BTG2 as being more highly expressed in individuals diagnosed as having schizophrenia relative to healthy controls by demonstrating a statistically higher level of RNA. The statistical significance of the differential expression of BTG2 is evidenced by its P value of 0.0076, as listed in Example 27 (Table 3Y). Therefore the Applicant has taught that there is a significant difference in differential expression for BTG2 as between a population of individuals having schizophrenia and a population of individuals not having schizophrenia, and further has taught to compare the level of expression of BTG2 in a test individual with populations having schizophrenia and populations not having schizophrenia using classification methods to determine the similarity or difference in gene expression levels as between the test subject and the tested populations (see paragraphs [0127] to [0129] and [0131] to [0136] in addition to [0412].

Furthermore, the Applicant contends that it does not require undue experimentation for one of skill to determine the inherent direction or level of the statistically significant differential expression required for the claimed methods of detecting a schizophrenia, given the widely established and validated analytical tools for analyzing gene expression levels. Therefore, it is not necessary for the Applicant to have taught the exact direction or level of difference between the two populations for one of skill to practice the invention. The Applicant has provided

sufficient information by teaching that there BTG2 is differentially expressed and that the differential expression between healthy and control subjects is significant as between the populations.

Nevertheless, in the interest of expediting prosecution of the instant application, Applicant has provided newly added claims which limit the differential expression to a higher expression in disease subjects with a fold-change of at least 2, in accordance with the data presented in Example 27 and Table 3Y of the specification. Further Applicant 's newly added claims recite that the differential expression be statistically significant by requiring that the P value be less than 0.5.

The Office Action also contends that the claims are not enabled due to unpredictability in the art on the grounds that Tsuang *et al.* teaches experiments which are similar to those of the specification relating to schizophrenia. Using microarray analysis, Tsuang *et al.* found that schizophrenia exhibited a unique expressed genome signature, allowing discrimination between the schizophrenia, BPD, and control groups. In addition, Tsuang et al. validated changes in several potential biomarker genes for schizophrenia and BPD by RT-PCR. Though Tsuang et al. teaches that such experiments must be interpreted with caution due to various potential limitations, Applicant respectfully submits, however, that the teachings of Tsuang *et al.* nevertheless clearly support the experimental data disclosed herein as being reliable, and further corroborate Applicant's disclosed data. In particular, Tsuang *et al.* clearly teaches that the results are most likely reliable despite the limitations cited by the Examiner, in accordance with the citation: "*Despite these limitations, this work demonstrates the potential utility of blood-based RNA profiling as a diagnostic tool...*" (concluding paragraph of Tsuang *et al.*). Applicant submits the term "potential" merely refers to the infancy of commercial diagnostics for schizophrenia, and does not refer to the reliability or predictability of such diagnostic methods. Applicant further submits that the experimental results disclosed in Tsuang *et al.* should enjoy a strong presumption of validity in view of this reference being a high-level and peer-reviewed academic publication. Applicant wishes to point out that the cautionary statements set forth in Tsuang *et al.* which were cited by the Examiner clearly represent a maximally conservative interpretation of the data, in line with the maximally conservative standards, for example, of the U.S. FDA for approval of novel medical applications to humans. The Applicant respectfully

indicates that it is improper to incorporate the standards for use by the FDA for purposes of determining patentability (see for example Application of Anthony, 56 C.C.P.A. 1443, 414 F.2d 1383, 162 U.S.P.Q. (BNA) 594 (1969); "*We believe that Congress has recognized this problem and has clearly expressed its intent to give statutory authority and responsibility in this area to Federal agencies different than that given to the Patent Office. This is so because the standards established by statute for the advertisement, use, sale or distribution of drugs are quite different than the requirements under the Patent Act for the issuance of a patent.*"

The office action further contends that BTG2 expression in blood may not be indicative of schizophrenia on the grounds that Dangonde *et al.* teach that BTG2 is differentially expressed in blood samples from MS patients relative to healthy controls, and Pittman et al. teach that BTG2 is differentially expressed in blood samples from RA patients relative to healthy controls. MS, RA and schizophrenia are very different diseases presenting disparate symptoms. Applicant contends that one of skill could distinguish schizophrenia from MS or RA, especially when the test subject is suspected of having schizophrenia, as recited in claim 112.

Applicant notes that even the much litigated patented method claims of Metabolite Laboratories, Inc.'s U.S. Patent No. 4,940,658, ('658), include method steps which can be used to indicate a disease or disorder other than the disease/disorder recited. For example, Claim 13 of '658 is drawn to a method for detecting a deficiency of cobalamin or folate in warm-blooded animals by assaying a body fluid for an elevated level of total homocysteine, and is thus used as a method to detect vitamin deficiency. However, it was well known in the medical community before the filing of '658, that the assay for elevated homocysteine levels could signal an increased risk of heart disease. Despite much scrutiny for other reasons, claim 13 of '658 has not been invalidated as a result of other previously known use(s) of its claimed assay to provide a correlation to a second disease or disorder not recited in its claim 13.

The Examiner also argues, on the basis of post-filing art of Wu (2001) and Newton (2001), that many factors may influence the outcome of the data analysis and notes that conclusions depend on the methods of data analysis. While considerations such as variability, and normalization are of importance, these considerations are well understood by a person skilled in the art and have been applied for many years to permit development of biomarkers

which are indicative of disease. These challenges are well understood, as are the routine experiments required to exemplify statistically significant differences in populations.

In summary, Applicant believes there is sufficient guidance provided by the specification and that the art is sufficiently predictable such that the amount of experimentation to perform the subject matter within the instant claims is not undue.

In view of the remarks and claim amendments, Applicant respectfully requests reconsideration and withdrawal of the rejection of the instant claims.

Conclusion

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. No new matter is added. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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